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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
Venkataraman BRINGI et al.	)	Group Art Unit: 1651
	)	
Application Number: 09/083,198	)	Examiner: I. MARX
	)	
Filed: May 22, 1998	)	
	)	

For: ENHANCED PRODUCTION OF TAXOL AND TAXANES BY CELL CULTURES OF *TAXUS* SPECIES

SUPPLEMENT TO SUBMISSION OF MARCH 19, 2002

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Commissioner for Patents
U.S. Patent and Trademark Office
Washington, D.C. 20231

Sir:

Applicants hereby submit the attached passages from "The Merck Index, 12th edition, pages 365 and 986. These pages were inadvertently omitted from the Submission filed on March 19, 2002.

Applicants believe that the application is now in condition for allowance, and a Notice to that effect is earnestly solicited.

No fee is believed to be required for this submission. However, in the event any fee is deemed necessary for consideration of all materials submitted in response to the most recent Office Action, the Commissioner is authorized to charge the undersigned's Deposit Account No. 50-1640.

Respectfully submitted,

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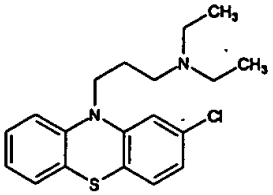
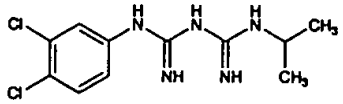
propyl)phenothiazine; 3-chloro-10-(3-diethylaminopropyl)-phenothiazine; RP-4909. $C_{19}H_{23}ClN_2S$; mol wt 346.92. C 65.73%, H 6.68%, Cl 10.22%, N 8.07%, S 9.24%. Prepn: Buisson *et al.* U.S. pat. 2,769,002 (1956 to Rhône-Poulenc).



Hydrochloride, $C_{19}H_{23}ClN_2S.HCl$, *Neuriplege.* Crystals, mp 178°. (Free base bp_1 225-240°). Sensitive to light. Soly in water about 1.0 g/60 ml, ethanol about 1.0 g/300 ml, chloroform 1.0 g/5 ml. Practically insol in acetone, ether, benzene. pH of 1% aq soln 4.8.

THERAP CAT: Muscle relaxant (skeletal); antipsychotic.

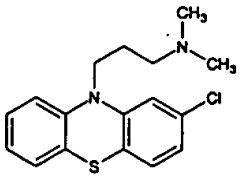
2237. Chlorproguanil. *N-(3,4-Dichlorophenyl)-N'-(1-methylethyl)imidodicarbonimidic diamide; 1-(3,4-dichlorophenyl)-5-isopropylbiguanide;* N^1-3,4-dichlorophenyl-N^5-isopropylbiguanide; N^1-3,4-dichlorophenyl-N^5-isopropyldiguanide; M-5943. $C_{11}H_{15}Cl_2N_5$; mol wt 288.18. C 45.85%, H 5.25%, Cl 24.60%, N 24.30%. Method of prepn: Crowther *et al.*, *J. Chem. Soc.* 1951, 1780; Curd *et al.*, U.S. pat. 2,544,827 (1951); Crowther *et al.*, Brit. pat. 667,116 (1952) (both to ICI).



Hydrochloride, $C_{11}H_{15}Cl_2N_5.HCl$, *Lapudrine.* Crystals, mp 246-247°. Soly in water: 1 g/100 ml. Solns may be boiled without dec.

THERAP CAT: Antimalarial.

2238. Chlorpromazine. *2-Chloro-N,N-dimethyl-10H-phenothiazine-10-propanamine; 2-chloro-10-(3-dimethylaminopropyl)phenothiazine;* 3-chloro-10-(3-dimethylaminopropyl)phenothiazine; *N*-(3-dimethylaminopropyl)-3-chlorophenothiazine; 2601-A; HL-5746; RP-4560; SKF-2601-A; Chlorderazin; Chlorpromados; Contomin; Esmind; Fenactil; Novomazina; Promactil; Prozil; Plegomazin; Sanopron; Aminazine; Ampliactil; Amplictil; Promazil; Proma; Elmarin; Wintermin. $C_{17}H_{19}ClN_2S$; mol wt 318.87. C 64.03%, H 6.01%, Cl 11.12%, N 8.79%, S 10.06%. Prepn: Charpentier *et al.*, *Compt. Rend.* 235, 59 (1952); Charpentier, U.S. pat. 2,645,640 (1953 to Rhône-Poulenc). Effects of neuroleptics on dopamine receptors: N.-E. Anden *et al.*, *Eur. J. Pharmacol.* 11, 303 (1970). Toxicity study: E. I. Goldenthal, *Toxicol. Appl. Pharmacol.* 18, 185 (1971). Review of analytical methods for determn in pharmaceutical prepns: L. F. S. Chagonda, J. S. Millership, *J. Pharm. Biomed. Anal.* 7, 271-278 (1989). Brief historical review: G. Curzon, *Trends Pharmacol. Sci.* 11, 61-63 (1990).



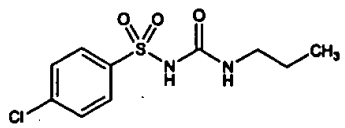
Oily liq. Amine odor. Alkaline reaction. $bp_{0.8}$ 200-205°. Maleate, *Clordelazin.*

Hydrochloride, $C_{17}H_{19}ClN_2S.HCl$, *Hebanil, Hibanil, Hibernal, Klorpromex, Largactil, Largaktyl, Megaphen, Promacid, Chloractil, Chlorazin, Sonazine, Marazine, Propaphenin, Taroctyl, Thorazine, Torazina.* Crystals, dec 179-180° (capillary); 194-196° (microblock). uv curve: Neuhoff, Auterhoff, *Arch. Pharm.* 288, 400 (1955). pH of 5% aq soln 4.0-5.5. One gram dissolves in 2.5 ml water. Sol in methanol, ethanol, chloroform. Practically insol in ether, benzene. Slightly acid to litmus. LD_{50} orally in rats: 225 mg/kg (Goldenthal).

THERAP CAT: Antiemetic; antipsychotic.

THERAP CAT (VET): Antiemetic; tranquilizer.

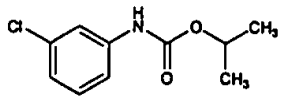
2239. Chlorpropamide. *4-Chloro-N-[(propylamino)-carbonyl]benzenesulfonamide; 1-(p-chlorophenylsulfonyl)-3-propylurea;* 1-(*p*-chlorobenzenesulfonyl)-3-propylurea; *N*-propyl-*N'*-(*p*-chlorobenzenesulfonyl)urea; P-607; Adiaben; Asucrol; Catanil; Chloronase; Diabechlor; Diabenal; Diabetoral; Diabinese; Melitase; Millinese; Oradian; Stabinol. $C_{10}H_{13}ClN_2O_3S$; mol wt 276.74. C 43.40%, H 4.73%, Cl 12.81%, N 10.12%, O 17.34%, S 11.59%. Prepn: Marshall, Sigal, *J. Org. Chem.* 23, 927 (1958); Brit. pat. 853,555; W. M. McLamore, U.S. pat. 3,349,124 (1960, 1967 both to Pfizer); Bauer *et al.*, *J. Org. Chem.* 31, 3440 (1960). Pharmacology and metabolism: Khurana *et al.*, *Indian J. Med.* 55, 1084 (1967); Brotherton *et al.*, *Clin. Pharmacol. Ther.* 10, 505 (1969); Madsen *et al.*, *Eur. J. Pharmacol.* 13, 374 (1971). Toxicity study: E. I. Goldenthal, *Toxicol. Appl. Pharmacol.* 18, 185 (1971).



Crystals from dil ethanol, mp 127-129°. uv max (0.01*N* HCl): 232.5 nm (ε 16500). Soly in water at pH 6: 2.2 mg/ml. Practically insol at pH 7.3. Sol in alc; moderately sol in chloroform; sparingly sol in ether, benzene. LD_{50} i.p. in rats: 580 mg/kg (Goldenthal).

THERAP CAT: Antidiabetic.

2240. Chlorpropham. *(3-Chlorophenyl)carbamic acid 1-methylethyl ester; m-chlorocarbanilic acid isopropyl ester;* isopropyl-*m*-chlorocarbanilate; isopropyl *N*-(3-chlorophenyl)carbamate; chloro-IPC; chloropropham; CIPC; Chlor-IFC; Furloe; Sprout-Nip. $C_{10}H_{12}ClNO_2$; mol wt 213.66. C 56.21%, H 5.66%, Cl 16.59%, N 6.56%, O 14.98%. Prepn: E. D. Witman, U.S. pat. 2,695,225; Strain, U.S. pat. 2,734,-911 (1954, 1956 both to Columbia-Southern Chem.); Brockway, U.S. pat. 2,806,051 (1957 to B. F. Goodrich). Toxicology: E. M. Boyd, E. Carsky, *Arch. Environ. Health* 19, 621 (1969).



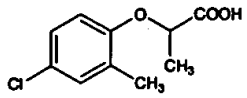
Solid, mp 40.7-41.1°. bp_2 149°. n_D^{20} 1.5388. Commercial product is a liquid. Slightly sol in water; miscible with most oils and organic solvents. LD_{50} orally in rats: 1.2 g/kg (Boyd, Carsky).

USE: Herbicide; plant growth regulator.

2241. Chlorprothixene. *3-(2-Chloro-9H-thioxanthen-9-ylidene)-N,N-dimethyl-1-propanamine; 2-chloro-N,N-dimethylthioxanthene-*$\Delta^{9,\gamma}$*-propylamine;* 2-chloro-*N,N*-dimethyl-3-thioxanthen-9-ylidenepropylamine; 2-chloro-9-(3'-dimethylaminopropylidene)thioxanthene; α-2-chloro-10-(3-dimethylaminopropylidene)thiaxanthene; N-714; Taractan; Truxal; Truxaletten; Tarasan. $C_{18}H_{18}ClNS$; mol wt 315.87. C 68.45%, H 5.74%, Cl 11.22%, N 4.43%, S 10.15%. Prepn: Brit. pat. 829,763 and Sprague, Engelhardt, U.S. pat. 2,-951,082 (both 1960 to Merck & Co.); Brit. pat. 834,143 (1960 to Am. Cyanamid). Comprehensive description: B. C. Rudy, B. Z. Senkowski, in *Analytical Profiles of Drug Substances* vol. 2, K. Florey, Ed. (Academic Press, New York, 1973) pp 63-84.

$(CH_3O)_2C_6H_2COOH$. The acid itself is unstable, rapidly changing to lactone.

5826. Mecoprop. *(±)-2-(4-Chloro-2-methylphenoxy)-propanoic acid; (±)-2-[(4-chloro-o-tolyl)oxy]propionic acid;* mechlorprop; MCPP; CMPP; RD-4593; Astix CMPP; Iso-Cornox; Compitox; Compitox Plus; Proponex-Plus. $C_{10}H_{11}ClO_3$; mol wt 214.65. C 55.96%, H 5.17%, Cl 16.52%, O 22.36%. Prepn: M. E. Synerholm, P. W. Zimmerman, *Contrib. Boyce Thompson Inst.* **14**, 91 (1945). Studies on plant growth regulation: C. H. Fawcett *et al., Ann. Appl. Biol.* **40**, 231 (1953); and comparison of enantiomers: M. Matell, *Kungl. Lantbruks-Hogsk. Ann.* **20**, 207 (1953); B. Aberg, *ibid.* 241. GLC determn: H. G. Higson, D. Butler, *Analyst* **85**, 657 (1960). Crystal structure: G. Smith *et al., Acta Crystallogr.* **B36**, 992 (1980). Herbicidal activity: G. B. Lush, *Proc. 3rd Brit. Weed Contr. Conf.* 625 (1956); E. L. Leafe, *ibid.* 633; B. Wallgren, *Weeds Weed Contr.* **24th** *Swedish Weed Conf.* 30 (1983); of (+)-enantiomer: J. Toll, *Weeds Weed Contr.* **28th** *Swedish Weed Conf.* 100 (1987). Degradation in soils: L. Lindholm *et al., Acta Agr. Scand.* **32**, 429 (1982); A. E. Smith, *Bull. Environ. Contam. Toxicol.* **34**, 656 (1985). Toxicological studies: M. R. Gurd *et al., Food Cosmet. Toxicol.* **3**, 883 (1965); H. G. Verschuuren *et al., Toxicology* **3**, 349 (1975); R. Roll, G. Matthiaschk, *Arzneimittel-Forsch.* **33**, 1479 (1983). EC-GLC determn in tissues and biological fluids: J. De Beer *et al., Vet. Hum. Toxicol.* **21**, Suppl., 172 (1979). HPLC resolution of enantiomers: B. Blessington *et al., J. Chromatog.* **396**, 177 (1987).



Solid, mp 93-94°. LD_{50} in rats (mg/kg): 1210 orally, 402 i.p. (Verschuuren).

(+)-Form, *Mecoprop-P,* ˚*Duplosan KV.* Solid, mp 95-96°. $[\alpha]_D^{25}$ +19° (alcohol).

Sodium salt, $C_{10}H_{11}ClNaO_3$. LD_{50} i.p. in rats, mice: 500, 600 mg/kg; orally in mice: 650 mg/kg (Gurd).

Diethylamine salt, $C_{14}H_{22}ClNO_3$, *Mecopar.* LD_{50} in rats, mice (mg/kg): 1060 ±120, 600 ±35 orally; 350, 400 i.p. (Gurd).

Potassium salt, $C_{10}H_{11}ClKO_3$, *Mecomec, Hedonal MCPP.*

USE: Herbicide.

5827. Mecrylate. *2-Cyano-2-propenoic acid methyl ester; 2-cyanoacrylic acid methyl ester;* methyl 2-cyanoacrylate; methyl α-cyanoacrylate; AD/here; Coapt. $C_5H_5NO_2$; mol wt 111.10. C 54.05%, H 4.54%, N 12.61%, O 28.80%. $CH_2{=}C(C{\equiv}N)COOCH_3$. Prepn: McKeever, U.S. pat. **2,912,454** (1959 to Rohm & Haas); McKeever, Raterink, U.S. pat. **2,926,188** (1960 to Rohm & Haas).

Liquid, $bp_{1.5}$ 47-49°. n_D^{25} 1.443.

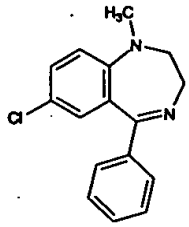
USE: Manuf of polymers and adhesives, *see* U.S. pats. **2,776,232** and **2,794,788** (1957 to Eastman Kodak). Surgical aid (tissue adhesive).

5828. Mecysteine Hydrochloride. *L-Cysteine methyl ester hydrochloride;* methyl cysteine hydrochloride; methyl β-mercaptoalanine hydrochloride; methyl α-amino-β-mercaptopropionate hydrochloride; LJ-48; Acdrile; Visclair. $C_4H_{10}ClNO_2S$; mol wt 171.65. C 27.99%, H 5.87%, Cl 20.65%, N 8.16%, O 18.64%, S 18.68%. $HSCH_2CH(NH_2)$-$COOCH_3$.HCl. Prepn: Bergmann, Michalis, *Ber.* **63**, 987 (1930); Zervas, Theodoropoulos, *J. Am. Chem. Soc.* **78**, 1359 (1956).

Crystals from methanol, mp 140-141°. $[\alpha]_D^{20}$ −2.9° (methanol).

THERAP CAT: Mucolytic.

5829. Medazepam. *7-Chloro-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepine;* Ansilan; Diepin; Medazepol; Megasedan; Narsis; Nobrium; Psiquium; Resmit; Rudotel; Tranquilax. $C_{16}H_{15}ClN_2$; mol wt 270.76. C 70.98%, H 5.58%, Cl 13.09%, N 10.35%. Prepn: L. H. Sternbach *et al., J. Org. Chem.* **28**, 2456 (1963); G. A. Archer *et al.,* Belg. pat. **620,773**, *C.A.* **59**, 10095b (1963); E. Reeder, L. H. Sternbach, U.S. pat. **3,243,427** (1963, 1966 both to Hoffmann-La Roche); S. Inaba *et al., Chem. Pharm. Bull.* **20**, 1628 (1972); M. Mihalic *et al., J. Heterocycl. Chem.* **14**, 941 (1977). Pharmacology: L. O. Randall *et al., Arch. Int. Pharmacodyn. Ther.* **185**, 135 (1970). Crystal structure: G. Gilli *et al., Acta Crystallogr.* **B34**, 3793 (1978).



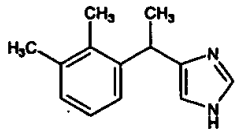
Colorless prismatic crystals from ether + petr ether, mp 95-97°. LD_{50} in mice (mg/kg): 360 i.p., 1070 orally (Randall).

Hydrochloride, $C_{16}H_{15}ClN_2$.HCl, orange-red crystalline powder. Freely sol in water, alcohol.

Note: This is a controlled substance (depressant) listed in the U.S. Code of Federal Regulations, Title 21 Part 1308.14 (1995).

THERAP CAT: Anxiolytic.

5830. Medetomidine. *4-[1-(2,3-Dimethylphenyl)ethyl]-1H-imidazole;* (±)-4-(α,2,3-trimethylbenzyl)imidazole; 4-[(α-methyl)-2,3-dimethylbenzyl]imidazole. $C_{13}H_{16}N_2$; mol wt 200.28. C 77.96%, H 8.05%, N 13.99%. α_2-Adrenergic agonist. Prepn: A. J. Karjalainen *et al.,* Brit. pat. Appl. **2,101,114**; A. J. Karjalainen, K. O. A. Kurkela, U.S. pat. **4,544,664** (1983, 1985 both to Farmos). Receptor binding study: R. Virtanen *et al., Eur. J. Pharmacol.* **150**, 9 (1988). Sedative and cardiovascular effects in humans: M. Scheinin *et al., Brit. J. Clin. Pharmacol.* **24**, 443 (1987). Veterinary evaluation in cats: D. Stenberg *et al., J. Vet. Pharmacol. Ther.* **10**, 319 (1987).

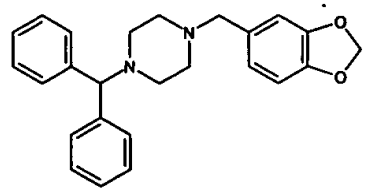


Hydrochloride, $C_{13}H_{16}CN_2$.HCl, *MPV-785, Domitor.*

d-Form, *dexmedetomidine, (S)-medetomidine, MPV-1440.* Pharmacokinetics: K. T. Kivisto *et al., Eur. J. Clin. Pharmacol.* **46**, 345 (1994). Clinical evaluation as surgical premedicant: M. Virkkila *et al., Anaesthesia* **49**, 853 (1994).

THERAP CAT (VET): Sedative; analgesic.

5831. Medibazine. *1-(1,3-Benzodioxol-5-ylmethyl)-4-(diphenylmethyl)piperazine; 1-(diphenylmethyl)-4-piperonylpiperazine;* 1-benzhydryl-4-piperonylpiperazine. $C_{25}H_{26}N_2O_2$; mol wt 386.49. C 77.69%, H 6.78%, N 7.25%, O 8.28%. Prepn: Belg. pat. **616,371**; Regnier *et al.,* U.S. pat. **3,119,826** (1962, 1964, both to Science Union). Pharmacology: Laubie *et al., Arch. Int. Pharmacodyn. Ther.* **151**, 313 (1964); Laubie, Schmitt, *ibid.* **155**, 1 (1965).



Dihydrochloride, $C_{25}H_{26}N_2O_2$.2HCl, *Vialibran.* Solid, mp 288°.

THERAP CAT: Vasodilator (coronary); bronchodilator.

5832. Medicagol. *3-Hydroxy-6H-[1,3]dioxolo[5,6]benzofuro[3,2-c][1]benzopyran-6-one;* 7-hydroxy-11,12-(methylenedioxy)coumestan; 7-hydroxy-5',6'-methylenedioxybenzo-